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Editorial Articles

A practical approach to diagnosing and treating infertility by the generalist in obstetrics and gynecology

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Summary

Purpose: To present a diagnostic and treatment paradigm for infertility designed for the obstetrician gynecologist generalist. *Materials and Methods:* Simple methods of tubal evaluation, e.g., the hysterosalpingogram (HSG) and post-coital test to evaluate both male and cervical factor are discussed. Treating paradigms will be discussed for ovulatory disorders and luteal phase defects. The role of the OB/GYN generalist on performing surgery in the modern era will be mentioned. *Results:* If an HSG shows a unilateral hydrosalpinx the generalist should consider performing the unilateral salpingectomy since the advent of in vitro fertilization-embryo transfer (IVF-ET) with a de-emphasis on surgery has made the reproductive endocrinologist/infertility specialist (REI) less skillful in laparoscopic surgery. The REI rarely performs tuboplasty today. Not only does the exclusive treatment in the luteal phase with progesterone save the women money and side effects (including multiple births), but may actually improve pregnancy rates compared to the usual technique of follicle stimulating drugs plus intrauterine insemination. *Conclusions:* Because the generalist will not be tempted to suggest therapies, e.g., IVF-ET because this effective therapy is the best option for the financial success of the REI, but at the expense of financial depletion of the patient, there is plenty of room for generalists taking over as the first line physicians for infertility rather than just a referral service. Reproductive endocrinologists/infertility will almost invariably perform IUI each month even if not doing IVF which is also profitable to the REI, but costly in time and money to the patient. In contrast, the generalist, aimed with the knowledge that IUI does not improve pregnancy rates if the post-coital test is normal, will save the patient and/or the insurance money if the woman conceives. Obviously certain circumstances, e.g., bilateral blocked fallopian tubes or very severe oligoasthenozoospermia (but not teratozoospermia) will prompt an immediate referral to an REI.

Key words: Post-coital test; Progesterone therapy; Laparoscopic surgery; Salpingectomy; Follicle maturing drugs.

Introduction

The obstetrician/gynecologist generalist is frequently the main primary care physician for women. Many generalists list their practice as OB/GYN and infertility. It is reasonable for the OB/GYN specialist to offer infertility services initially rather than an automatic referral to a specialist in reproductive endocrinology and infertility (REI) similar to the primary care physician or general internist having the right to treat a person for probable peptic ulcer disease without an immediate referral to the gastroenterologist or treat a person for a urinary tract infection without immediately referring the patient to a nephrologist or infectious disease specialist. Of course if the problem is not corrected in a reasonable amount of time then a referral to the specialist in that field would be a reasonable approach.

The objective of this editorial is to try to provide a practical diagnosis and treatment philosophy for the OB/GYN generalist to attain the goal of a successful pregnancy that is within the scope of reasonable diagnostic and treatment "tools" available to the generalist. Furthermore this manuscript will try to provide a philosophy that will help the generalist to determine the appropriate infertility specialist to whom to refer the couple if the generalist is unsuccessful in helping the couple to achieve a pregnancy. Finally the guidelines will be provided so that the generalist will know when is the right time for the referral to an REI, i.e., what is a reasonable time for a given treatment before more involved procedures are needed.

Evaluating and treating fallopian tube and pelvic pathology

The most common cause of infertility around the world is damaged fallopian tubes. This is most commonly caused by

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previous sexually transmitted diseases with adhesions from endometriosis as the next most common factor.

The usual first type of investigation for tubal disease is the hysterosalpingogram (HSG). The sonohysterogram does not provide an adequate assessment of the fallopian tubes though is very good for evaluating uterine cavity abnormalities.

Though patent fallopian tubes do not necessarily negate a pelvic mechanical factor, e.g., phimosis of the fimbria, or tubal or ovarian adhesions interfering with tube oocyte pick-up, most REIs will not proceed to a laparoscopy at this point if the fallopian tubes appear normal but seek another remediable infertility factor.

If a laparoscopy is the next logical procedure to be performed, years ago, the REIs had more extensive training in laparoscopic surgery than the generalist. Today when I review the charts of patients seeking another opinion concerning their unsolved infertility problem I usually find that the previous REIs have not suggested a laparoscopy but rather always seems to push their patients toward in vitro fertilization-embryo transfer (IVF-ET). This means that REIs, and especially the fellow in REI, are becoming less skilled in performing laparoscopic surgery. Unfortunately this push away from laparoscopy and toward IVF-ET may be financially motivated. Thus fellows are no longer trained in intricate tubal microsurgery and thus there has been a tendency for less surgically skilled but more cerebral type OB/GYN residents seeking fellowships in REI. Thus it is probably time that there is a shift toward the generalist rather then the REI performing laparoscopy for infertility. The obstetrics/gynecologist generalist interested in the field of infertility should take extra training in laparoscopy surgery to become the surgical successors. Of course at the same time they should get extra training in hysteroscopic surgery.

The gynecologist should be aware that when faced with bilateral hydrosalpinges during laparoscopy, the physician should be prepared to preferably perform a bilateral salpingectomy because the infectious material in these diseased fallopian tubes can infiltrate the uterine cavity and prevent implantation with IVF-ET [1-3].

Some clinicians were under the impression that as long as one tube was open that salpingectomy is not needed, but it has been established that even a unilateral hydrosalpinx can impair fertility and it should be removed [4]. One case showed that removing a unilateral hydrosalpinx can allow pregnancy through natural conception as long as the other fallopian tube is normal even if she previously failed to conceive after several cycles of IVF-ET [5]. If the "non-diseased" fallopian tube is impaired by adhesions, the gynecologist should have sufficient skill to lyse the adhesions to free the fallopian tube.

On the other hand, the gynecologist should be aware that if the contralateral fallopian tube is a hydrosalpinx and is patent but involved with adhesions, one can also choose to lyse adhesions hoping that the patency of the tube allows escape of infectious material rather than infiltrating the uterine cavity [6]. However, the gynecologist should also be aware that not removing the "patent" hydrosalpinx would markedly increase the risk of ectopic pregnancy. Furthermore, even a patent hydrosalpinx can impede IVF-ET success. Thus a pre-op consultation is needed where the patient is presented the data and a decision is made as to salpingectomy or not. This decision could be predominantly based on the patient's insurance and financial means as to whether IVF-ET is a possibility or not as to the type of surgery performed.

Complete salpingectomy is preferred to not only enhance fertility potential, but to prevent subsequent ectopic pregnancies even with IVF-ET. However on occasion, especially related to the presence of dense adhesions, salpingectomy is not feasible, and therefore a tubal ligation is performed to at least impede infiltration of infectious material to the uterine cavity.

The majority of women with endometriosis can conceive by correcting ovulatory dysfunction [7]. Since attempts at removing endometriosis can lead to a diminished ovarian reserve, it is probably best not to perform a laparoscopy initially even if endometriosis is suspected by symptoms or signs. Nevertheless there are data suggesting that at least in some women, and as in those who fail to conceive after correcting luteal phase defects or the luteinized unruptured follicle (LUF) syndrome, removing endometriosis through laparoscopy can improve fecundity [8-11].

At one time the REI was more skilled than the generalist in performing laparoscopic surgery. Today probably because IVF-ET results in a quicker and more definite pregnancy (but unfortunately also because performing IVF-ET is far more profitable to the REI than laparoscopic surgery). many REIs are not as skilled as in previous time in this surgical technique. Thus a skilled generalist should not be afraid to advise the patients that if simple measures performed by the generalist that will be further described in this editorial are not effective in achieving a pregnancy and the opinion of an REI is obtained, if the REI suggests IVF-ET, and this is not an affordable option, to make an appointment with the generalist to perform a laparoscopy with ablation of endometriotic implants and possible lysis of adhesions. Of course it is important for the generalist to be familiar with proper technique to not only maximally improve fertility outcome but also to relieve pain [12].

Ovulation disorders – women with regular menses

There are three phases of ovulation – attaining a mature dominant follicle (18-24 mm average diameter with a serum estradiol (E2) >200 pg/mL), releasing the oocyte from the follicle (as defined by shrinkage of the follicle by at least five mm two days after the LH surge), and the production of adequate progesterone (and E2 also) by the corpus luteum that is formed from the dominant follicle minus the oocyte [13].

There is evidence that a small majority of women who have infertility, regular menses, and have luteal phase de-

fects make mature follicles [14]. One study found that 77% of these women achieved a pregnancy in six months with just luteal phase progesterone support *vs.* only 17% with follicle maturing drugs [14]. Yet 64% of the failures who had taken follicle maturing drugs conceived when placed on progesterone support exclusively during the next six months [14].

Thus for infertile women with regular cycles, I usually will perform pelvic sonography to evaluate follicular size beginning 16 days before their earliest expected menses. If the follicle is ≥ 18 mm, a serum E2 will be obtained. If the follicle is less than 18 mm, they will be asked to return when the follicle is expected to reach 18 mm, considering that follicles grow at about two mm per day. If follicular maturation is reached two days later, a repeat ultrasound is performed to see if the oocyte released from the follicle [15]. If the follicle reached maturity and the oocyte released, the woman is treated exclusively with vaginal progesterone (progesterone vaginal suppositories 200 mg morning and bedtime, or Crinone vaginal gel 8% am or am and hs, or Endometrin vaginal tablets 100 mg twice or three times per day. One way to determine if the dosage of progesterone is sufficient is to perform a pelvic sonogram at mid-luteal phase. If the endometrial echo pattern did not convert to a homogeneous hyperechogenic pattern, the dosage of progesterone should be increased at that moment and the dosage started higher the next cycle [16]. What if the oocyte did not release? Studies show that failing to release the oocyte could be an isolated phenomenon. However, the majority of women who fail to release the oocyte the first time will fail in succeeding cycles [15]. Thus therapy with either a single injection of 10,000 units of human chorionic gonadotropin is given or if this fails leuprolide acetate (now using its agonistic effect to raise endogenous LH and FSH) one mg every 12 hours with two or three dosages [17].

At first glance the OB/GYN generalist may think that the proposed diagnostic paradigm presented above is beyond the scope of the generalist, but should be relegated to the infertility specialist. Unfortunately the aforementioned more scientific approach is not taken by most reproductive endocrinologists. Instead the majority seems to practice a type of scripted or universal treatment protocol that is not specifically geared to specific problems. Most might try even in women with regular menses three cycles of clomiphene citrate with intrauterine insemination (IUI), three cycles of FSH injection and IUI, and then push them into IVF-ET. Usually they do not prescribe progesterone in the luteal phase for IUI cycles, just IVF cycles.

Intrauterine insemination (IUI)

The best cervical mucus is about 40 hours before ovulation and coincides with the peak serum E2. Right at the time of ovulation the cervical mucus may have already regressed. So the theory holds that even if one has a normal post-coital test maybe the sperm lacks longevity of fertilization potential, so placing the sperm past the cervix directly into the uterine cavity so that there is a closer proximity to ovulation may help some women to achieve pregnancies. However, we presented data at the 2011 American Society of Andrology meeting showing a 25% pregnancy rate per cycle in couples with corrected infertility factors having normal post-coital tests without IUI *vs.* 26% with IUI added [18]. Thus there is the opportunity for a generalist interested in infertility to take over the cases that do not require IVF-ET. The generalist could do their own ultrasounds, either personally or with an ultrasound tech or could refer them to a local ultrasound facility. Similarly in the "old days" REIs had to develop their own endocrinology laboratory to get same-day results for serum estradiol, progesterone, LH, and FSH. Today all commercial laboratories provide this service. Suppose, however, the generalist is too busy to be able to deal with the day by day decisions that this paradigm requires. Yet, the generalist is reluctant to immediately refer to the REI because he is aware of the patient's limited finances and the generalist's experience is that the expensive aforementioned "shot-gun" approach with a push toward IVF-ET is the norm for the local REI specialist. It would be appropriate for the generalist to try limited treatment, described below aimed at improving the women's fertility potential, but with an educated guess as to what the problem may be. Thus this approach has potential to help with little potential to harm or diminish the couple's infertility problems.

Evaluating male factor and cervical factor

For couples where the female partners have regular menstrual cycles, the wife is asked to return 15 days before her earliest expected menstrual cycle having intercourse the night before. Finding any sperm moving in a forward manner through the cervical mucus will establish that there is probably not a sperm issue or cervical mucus problem. If the post-coital test is subpar one may have the couple try this again in two days. If still not good then a semen analysis can be ordered or the generalist could ask the couple to bring in a fresh specimen and after placing a drop of sperm on the slide with a coverslip, the generalist can get a reasonably good idea if there seems to be an adequate amount of sperm or not. If the sperm concentration of motile sperm seems reduced, the usual tendency is to refer to a general urologist or a fertility trained urologist. Some urologists will evaluate whether a varicocele is present and if so recommend varicocelectomy. There is little evidence that this procedure helps improve sperm count and motility [19]. Referral to the REI will generally lead to IUI then to IVF with intracytoplasmic sperm injection (ICSI) or directly to IVF with ICSI. However, if the generalist simply obtains a serum FSH and testosterone on the male partner finding an

FSH and testosterone level in the low to low normal range could lead to improvement of the sperm and pregnancy through normal intercourse, by simply treating the male partner with clomiphene citrate 25 mg daily and giving the couple up to six to eight months to achieve a pregnancy before referral to a urologist or REI [19]. Thus, to reiterate, if the post-coital test shows any sperm progressing in the cervical mucus at least eight hours after intercourse, it is probably sufficient not to obtain a formal semen analysis. Even if the sperm concentration falls below the low normal level of $\leq 10 \times 10^6$/mL, it does not necessarily mean that any treatment other than intercourse is necessary. We presented data that with natural intercourse infertile women achieved following correction of female infertility factors a 22% six-month pregnancy rate with less than 2.5×10^6/mL sperm concentration a respectable 69% pregnancy rate with 2.5 to $< 5 \times 10^6$/mL, 81% with 5 to $\leq 10 \times 10^6$/mL, and even 81% with those with 5 to $< 10 \times 10^6$/mL, which was equal to the pregnancy rate for those with superior sperm motile density of $> 15 \times 10^6$/mL [20]. Thus I think for the OB/GYN generalist it is appropriate to forego a formal semen analysis if the post-coital test is adequate, which means demonstrating at least one sperm moving across a few high powered fields. If a gynecologist wants, he/she can send out the first few semen specimens but place an aliquot of carefully mixed sperm on a slide and try to develop an educated guess as to the concentration and motility if the post-coital test is below par to gain insight as to whether the problem is a male factor or cervical factor. Of course the reader may question the soundness of this suggestion of sperm evaluation because it eliminates morphology. Indeed sperm morphology at one time was considered the best way to detect a subnormal male [21]. However, though we were a minority at that time, we challenged this test as being able to detect a subfertile male [22]. Indeed in the modern era most fertility centers do not place much value on this test [23-25]. Kruger's test for strict morphology uses 4% normal as the cut-off for detecting subfertile males. We have presented a scientific presentation at the 2012 American Society of Andrology meeting showing that even only 1% normal sperm does not adequately detect the subnormal male.

When we evaluate the male in our practice we always measure the hypo-osmotic swelling test and antisperm antibodies [25]. Most REIs do not assess these very important tests when they perform semen analyses. We will measure for antisperm antibodies on the sperm if the post-coital test is normal because a male may have antibodies that block the attachment of the sperm to the zona pellucida even if immobilizing antibodies are absent [26]. Nevertheless most times significant antisperm antibodies will be immobilizing antibodies and cause a poor post-coital test [26]. Subnormal HOS tests which allow fertilization but failure of the embryo to implant for some reason would not be evaluated by over 95% of REIs [27]. So if the couple fails after many months of treatment, a simple referral to an REI will still miss low HOS tests or antisperm antibodies so the OB/GYN generalist would be better served to find a laboratory that performs these tests and send the male partner there. Fortunately the frequency of this abnormality is only about 5% in males < 40, 16% in males 41-49, and 25% in males > 50 [27]. If the post-coital test is subpar and the semen analysis appears normal even by observation of a drop, and if the mucus appears to have subpar quality, checking the serum E2 and P levels can help the OB/GYN generalist to know if the timing was right. If so one could repeat the post-coital test the following month and one could treat the women with guaifenesin 600 mg extended release tablets twice daily from day 1 until ovulation to attempt to improve cervical mucus quality [28].

Anovulation

What about women who appear to be anovulatory based on oligomenorrhea or amenorrhea? A simple measurement of E2 and FSH can help the physician to determine if the woman appears to have adequate oocyte reserve. If so, for the OB/GYN generalist my recommendation would be to treat the women with letrozole rather then clomiphene citrate [29]. The main reason for this suggestion is that clomiphene citrate is more apt to create hostile cervical mucus [30]. Furthermore letrozole can sometimes enable women with polycystic ovarian syndrome, especially obese women, to ovulate when clomiphene citrate fails. Letrozole is less likely to adversely affect endometrial thickness [29]. Finally it is more likely to induce mono-follicular ovulation. If 2.5mg for five days does not induce ovulation, as evidenced by follicular maturation studies with ultrasound and measurement of serum E2 and P, the dosage can be increased to five mg per day. Sometimes one does not need to induce another menstrual cycle with medroxyprogesterone acetate but merely start the increased dosage if there is no evidence of ovulation within ten days of stopping the letrozole. It is still important to supplement the luteal phase with progesterone since there is usually persistent luteal phase defects and thus increased miscarriage risk in women taking follicular maturation drugs [31].

Women with diminished oocyte reserve

I think that for the OB/GYN generalist it is wise not to measure the day 3 serum FSH at all for fear this will panic the physician and prompt an immediate referral to an REI thinking that time is running out. This seems to be a very provocative statement so I will explain why I make this statement. The large majority of REIs are under the wrong impression that a high day 3 serum FSH or a low inhibin B or anti-Müllerian hormone level is predictive that a woman even if chronologically young, has oocyte quality more akin to perimenopausal women [31].

In vitro fertilization is considered the ultimate method of achieving a pregnancy in an infertile woman. As far back as 1988 a high day 3 serum FSH was found by one of the leading IVF centers in the world to be associated with poor responders to exogenous gonadotropin, and even more important, was the observation of very poor pregnancy rates even if normal appearing embryos were transferred [33].

Even with all of the recent improvements in IVF-ET in recent times, one of the world's leading IVF centers concluded that if the day 3 serum FSH ever exceeds 15 mIU/mL (even once), the live delivery rate is zero even after the transfer of normal appearing embryos [34]. However, we subsequently published data showing that despite the development of only one embryo in women whose serum FSH levels were all over 15 mIU/mL the clinical pregnancy rate was about 40% per transfer and the live delivered pregnancy rate 33% on the 65% who had a six- to seven-cell embryo [35]. The explanation for the dichotomy between these opposite conclusions is that the very poor pregnancy rate found in some IVF centers will was not as much related to extremely poor quality oocytes. but related to iatrogenic meiosis issues and downregulation of implantation factors by raising the serum FSH too high, by using high dosage FSH stimulation in an effort to create more follicles [35].

Mild stimulation, on the other hand results in pregnancy rates following IVF-ET in women with diminished oocyte reserve comparable to those women with normal reserve [36]. Despite our aforementioned publications which occurred in the same journal as the Roberts *et al.* article [34], most REIs when faced with a woman with increased FSH will try high-dose FSH with or without IVF or will try to convince the couple that they should go directly to donor oocytes. The OB/GYN generalist has a better chance of achieving a pregnancy with just luteal phase progesterone support. Indeed we found that with just progesterone support women with a serum FSH > 15 mIU/mL have at least half the chance of conceiving naturally as women with normal FSH [37]. The success rate would even be higher for women with less severe oocyte depletion yet even women with only mild diminished oocyte reserve are recommended to the donor oocyte program.

The manuscript suggests that because REIs seem to be most interested in IVF-ET, there is room for OB/GYN generalists interested in the fertility field to take over as the main healthcare provider to provide the initial evaluation and treatment of infertile women. If there is failure after a reasonable number of treatment cycles, then they should refer to an REI with the likelihood that IVF-ET is the next step.

Suggestions for a very busy OB/GYN generalist

For those OB/GYN generalists whose busy schedule precludes evaluating a given individual at specific given times of the schedule then the generalist should not offer clomiphene citrate but consider prescribing vaginal progesterone on the third day of temperature rise on a BBT especially in women ≥ 30 years of age. Doing just a little more would include performing an HSG and fitting the couple in for a one time post-coital test.

For those generalists who would rather not treat infertility at all it is hoped that this editorial will better enable the OB/GYN to refer to the REI that would be best suited for his/her patient. Certainly the OB/GYN generalist should be reluctant to refer a woman of less financial means and an insurance that does not cover IVF-ET to an REI whose tendency is to perform IVF-ET or practicing herd medicine (three cycles of clomiphene citrate and IU, three cycles FSH injections, and IUI then IVF-ET on everyone).

As the primary care physician of women, no matter what stage a referral was made to an REI, the generalist may tell the woman to make an appointment for a month or two after the initial consultation with the REI so that the generalist can help decide if the treatment paradigm suggested by the REI is more favorable for the patient or the REI. If not satisfied, the generalist may recommend a different REI for a second opinion.

It should be noted that methods of truly diagnosing inadequate progesterone therapy during the luteal phase have not been developed adequately. The future eventually will allow rapid measurement of an immunomodulatory protein known as the progesterone induced blocking factor (PIBF) which suppresses natural killer cell activity in the vicinity of the maternal fetal interface [38]. After normals are determined, women falling below a certain PIBF level will either be given progesterone or their dosage will be increased. Alternatively, evaluation of human endometrial genome of a biopsied specimen in the luteal phase may determine when there is a deficiency or alteration of gene targets that are present during the window of implantation that may influence successful implantation [39]. Until the time that these tests are commercially available, it is reasonable to empirically treat women with progesterone in the luteal phase, especially if the woman is ≥ age 30.

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